2) The Office Action maintains the rejection of Claims 1-6 under 35 USC §103 as being obvious over Hora et al (US #5,078,997), in view of Lee (US #5,656,730). (Office Action Item 4).

3) The Office Action maintains the rejection of claims 9 and 10 under 35 USC §103 as being obvious over Hora et al (USP #5,078997), in view of Nayar (USP #5,874,408).

4) The Office Action rejects Claims 1-6 and 10 under 35 USC 102 (a) as being anticipated by Shanafelt et al (WO 99/60128 A1).

RESPONSES

1. The Office Action alleges that the Declaration as filed was defective. (Office Action Item 2). Specifically, the Office Action states that "the oath or declaration is defective because all the inventors names have to be on the same sheet." As authority for this instruction, the Office Action cites M.P.E.P. §602.01 and §602.02.

Applicants respectfully traverse the requirement to submit a new oath or declaration. Neither 35 U.S.C. § 1.63, M.P.E.P. §602.01 nor M.P.E.P. §602.02 requires that all the inventor's names be on the same sheet of paper. More specifically, the second paragraph of §602.02 makes clear that the inventor's declarations may be on more than one sheet of paper. The approved declaration form provided by the US Patent Office, Form PTO/SB/01A (10-00), also makes clear that if needed, additional forms may be used and attached. It is also understood that if all 37 CFR 1.63 information is provided, an applicant may use any form as a Declaration Form.

For the reasons discussed above, applicants believe that the Declarations of the three inventors were not defective as alleged in the Office Action, and respectfully request that the Examiner withdraw this requirement.

2) The Office Action maintains the rejection of Claims 1-6 under 35 USC §103 as being obvious over Hora et al (USP #5,078,997), in view of Lee (USP #5,656,730). (Office Action Item 4).

Applicants respectfully traverse the Office Action's rejection of Claims 1- 6 under 35 U.S.C. §103 as being obvious over Hora et al, in view of Lee. The Office Action presents the argument that the present invention is simply another species of the larger genus of stabilized IL-2 compounds, and states that it would have been obvious to combine the teachings of Hora and Lee. However, **the Office Action is silent on the location of the suggestion in the prior art that would have motivated someone to combine the references**. As discussed below, the target molecules in the Lee and Hora patents are very different molecules, and a skilled practitioner in the art would not conclude that the technology applicable to one would obviously apply to the other. For example, IL-2 (Hora, and Wang) has a molecular weight of approximately 13,000 to 17,000 Daltons, while antibodies (Lee) can weigh upwards of 160,000 Daltons. IL-2 is a single molecule (with a small number of muteins) while there are many classes of animal antibodies (five major classes of human antibody plus a number of subclasses). Because of the differences in functionality, size, and structural variety, it is not obvious that the technology applicable to one would serve the same purpose for use with the other. For the Office to conclude that the application of antibody technology (Lee) would be of obvious use in the cytokine art (Hora) it would be necessary to identify a clear suggestion or motivation in the teachings. In §2144.08 (f) (5) of the M.P.E.P., the Office is instructed to "specifically articulate what teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus." No such information was provided. It is axiomatic to note that any conclusion of

obviousness may not be based upon improper hindsight reasoning, especially reasoning acquired from applicant's own disclosure. M.P.E.P. § 2145 (X) (*A*) In addition, an "obvious to try" rationale is support of an obviousness rejection is improper. M.P.E.P. § 2145 (X) (*B*)

The **Hora** patent discloses the stabilization of IL-2 using an arginine, carnitine, betaine mixture, a polyvinylpyrrolidone, sugars, salts of capric acid, and a buffer. **Hora states that the need for stabilization is that IL-2 is difficult to maintain in solution.**

The **Lee** patent discloses and claims a method of inhibiting the aggregation of an aqueous **monomeric single-chain antigen-binding protein** wherein the storage-stabilizing amount of sucrose, histidine or glycine added is sufficient to inhibit aggregation. The Lee patent states, "**Antibodies represent a specific class of proteins** generated by the immune system to provide a molecule capable of complexing with an invading molecule, termed an antigen. Natural antibodies have two identical antigen-binding binding sites, both of which are specific to a particular antigen. **The antibody molecule "recognizes" the antigen by complexing its antigen-binding sites with areas termed epitopes.** The epitopes fit into the conformational architecture of the antigen-binding sites of the antibody, enabling the antibody to bind to the antigen." **Lee goes on to state that "the terms "single-chain molecule" or "single-chain protein" are used interchangeably. They are structurally defined as a first polypeptide, comprising the binding portion of the variable region of an antibody heavy or light chain, associated with a second polypeptide, comprising the binding portion of the variable region of an antibody heavy or light chain, the two polypeptides being joined by a peptide linker linking the first polypeptide and second polypeptide into a single polypeptide chain.** The single polypeptide chain thus comprises a pair of variable regions connected by a polypeptide linker. **The regions may associate to form a functional antigen-binding site,** as in the case wherein the regions comprise a light-chain and a heavy-chain variable region pair with appropriately paired complementarity determining regions (CDRs). In such a case, **the single-chain protein is referred to as a "single-chain antigen binding protein"** or "single-chain antigen-binding molecule." A similar single-chain antigen-binding protein comprising multiple pairs of heavy and light

chain variable regions is also stated to be a part of the invention." The claims of the Lee patent are specifically limited to this class of **monomeric single-chain antigen-binding protein**.

The Office Action states that Hora et al. teach the stabilization of IL-2 with sugars, amino acids etc., and that Lee discloses the use of sucrose and histidine to stabilize "monomeric proteins". The Office Action then concludes its remarks by stating "therefore, the claims are obvious over Hora ... in view of Lee ... ." However, neither Hora nor Lee provides any suggestion as to how their compositions can be modified to act as a stabilizer for other molecules. In light of the very significant differences in the molecules disclosed by Lee and Hora, and in the purposes for molecule stabilization, it is difficult to understand why a skilled practitioner would look to Lee to improve the Hora technology.

To establish a prima facie case of obviousness under 35 U.S.C. §103, three criteria must be met. First, there must be some suggestion or motivation to combine the references, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all of the claim limitations. M.P.E.P. § 2142 The Office Action fails to comply with the first requirement to establish a prima facie case of obviousness under §103 by not identifying the specific location of any motivation to combine the references. Secondly, the Office Action is silent on the source or location of any suggestion to combine references that would provide a reasonable expectation of success if the combination were to be made. Therefore, a proper rejection of Claims 1-6 under §103 has not been established.

For all the reasons mentioned above, applicants traverse this rejection of Claims 1-6 under 35 USC §103 as being obvious over Hora et al (USP #5,078,997), in view of Lee (USP #5,656,730). Applicants respectfully ask the Examiner to reconsider this rejection in light of the information presented above and withdraw this rejection. In the event the Examiner does not agree that the rejection should be withdrawn, applicants request that the specific motivation to combine the cited references be identified.

3) The Office Action maintains the rejection of claims 9 and 10 under 35 USC §103 as being obvious over Hora et al (USP #5,078,997), in view of Nayar (USP #5,874,408).

Claims 9 and 10 of the present application are directed to a stable IL-2 composition comprising IL-2, histidine, NaCl, sucrose, and glycine at a pH of 5 to 6.5. The Hora patent discloses a stable IL-2 composition comprising an arginine, carnitine, betaine mixture, a polyvinylpyrrolidone, and salts of capric acid. **Hora does not disclose the use of histidine, glycine, or NaCl.** Additionally, Hora does not suggest the use of the disclosed materials for any other purpose. **Nayar discloses the use of glycine, histidine, sucrose, NaCl, and $CaCl_2$ to stabilize recombinant Factor VIII.** Nayar does not suggest the use of the recited materials for any other stabilization purpose. Of additional importance in this response, **Nayar does not suggest deleting one of the listed materials (note that the present application does not include $CaCl_2$) to stabilize any other molecule.**

In order to establish a prima facie case of obviousness under §103, the Patent Office must demonstrate that three criteria have been met. First, there must be some suggestion or motivation to combine the references, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all of the claim limitations. M.P.E.P. § 2142

The present Office Action does not disclose the source of the motivation(s) to combine the references, making it impossible to respond to the first requirement under §103. As was mentioned above, it is improper to base a rejection upon reasoning acquired from an applicant's own disclosure. M.P.E.P. § 2145 (X) (*A*) In addition, using an "obvious to try" rationale to support an obviousness rejection is improper. M.P.E.P. § 2145 (X) (*B*) Secondly, neither of the cited references provides any

"expectation of success" if the references were to be combined. And lastly, the prior art references would somehow have to be combined and then at least one essential element from the Nayar patent ($CaCl_2$) would have to be deleted. There most certainly is no suggestion in either of the references to delete essential components to make a new stabilizing compound. In fact, deletion of an element and retention of functionality is a clear indicia of unobviousness. M.P.E.P. §2144.04 (II)(B).

For all of the above-mentioned reasons, applicants respectfully request the Examiner to reconsider and withdraw this rejection of Claims 9 and 10. In the event the Examiner does not agree that the rejection should be withdrawn, applicants request that each of the specific elements of a rejection under §103 be identified with particularity.

4) The Office Action rejects Claims 1-6 and 10 under 35 USC 102 (a) as being anticipated by Shanafelt et al (WO 99/60128 A1).

A claim is anticipated under 35 U.S.C. §102(a) "if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. 2131 The Shanafelt patent discloses a composition of matter made up of IL-2 muteins, an IL-2 mutein in a pharmaceutical carrier, a cell transformed with the mutein polynucleotide, a vector containing the mutein polynucleotide, and various methods of using the mutein or its polynucleotide. **The present application discloses IL-2 stabilized with histidine.** Shanafelt discloses an IL-2 mutein containing a histidine substitution at position 20. **This Shanafelt histidine substitution** in the IL-2 mutein **is not the same thing as using histidine in combination with IL-2 as a stabilizing agent** (present application). A stabilizing agent **does not** act by a substitution mechanism with the molecule being stabilized. Shanafelt neither discloses nor claims an IL-2 stabilized with histidine. Therefore at least one essential element of the present application is missing in the referenced Shanafelt patent, and a 35 U.S.C. §102(a) rejection based upon that patent is improper.

For the reasons mentioned above, applicants respectfully traverse the rejection of Claims 1-6 and 10 under 35 U.S.C. §102(a) as being anticipated by Shanafelt, and request the Examiner withdraw this rejection.

In conclusion, applicants believe that Claims 1-6, 9 and 10 are in condition for allowance, and each of the grounds of objection and rejection has been addressed, and prompt issuance of the present case is earnestly solicited.

A completed form PTO/SB/22 Petition for Extension of Time under 37 C.F.R. 1.136(a) to extend the period for filing a response by two months is herewith submitted.

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call their Attorney at the phone number listed below.

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